



# Clinical Management of Hepatitis B

WAN-CHENG CHOW

DEPARTMENT OF GASTROENTEROLOGY & HEPATOLOGY

SINGAPORE GENERAL HOSPITAL

# The World Health Organisation recent initiatives on HBV infection

- ▶ Launching of the first “Guidelines for the prevention, care and treatment of persons living with chronic hepatitis B infection” in March, 2015.
- ▶ Adoption of the first “Global Health Sector Strategy on Viral Hepatitis 2016 – 2021” at the World Health Assembly in May, 2016.

Global targets to be achieved by 2030:

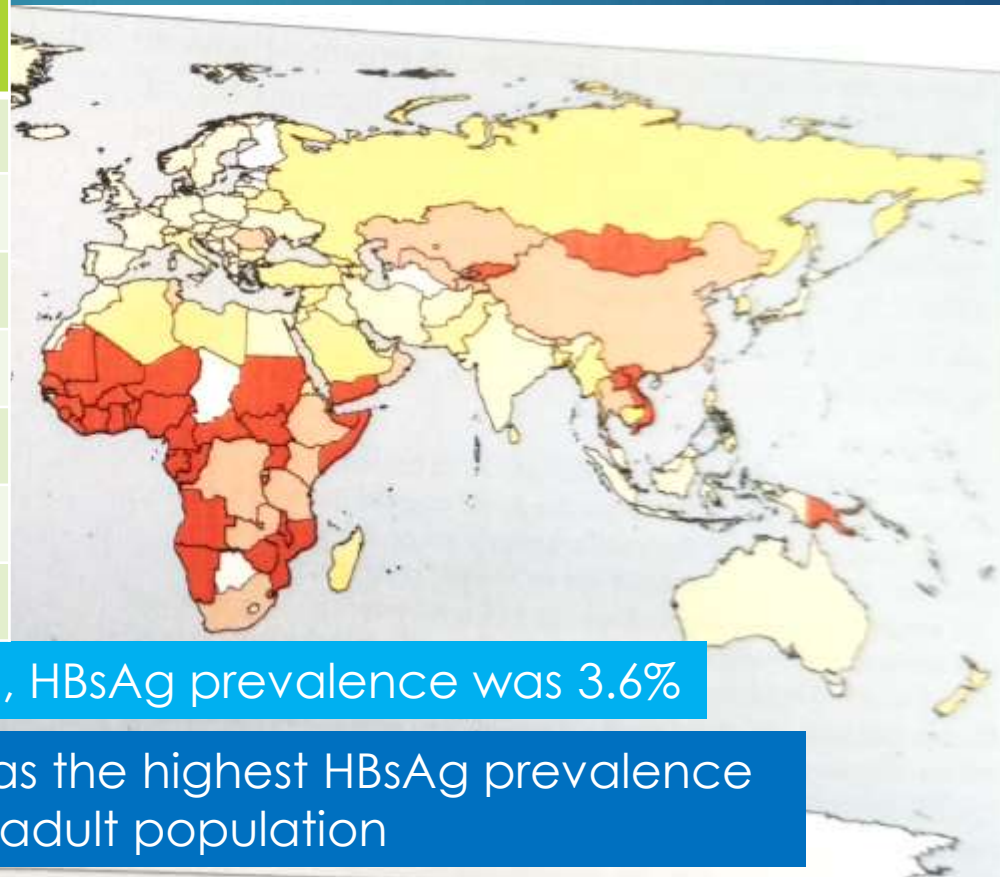
- ▶ reduction of new viral hepatitis infections by 90%
- ▶ Reduction of hepatitis B – related deaths by 65%

# Prevalence of chronic hepatitis B virus (HBV) infection (HBsAg +ve)

- based on systematic review of data between 1965 – 2013 (1800 / 4310 papers included in study)

## Prevalence dropped over two periods (1957 – 89 v.s. 1990 - 2013)

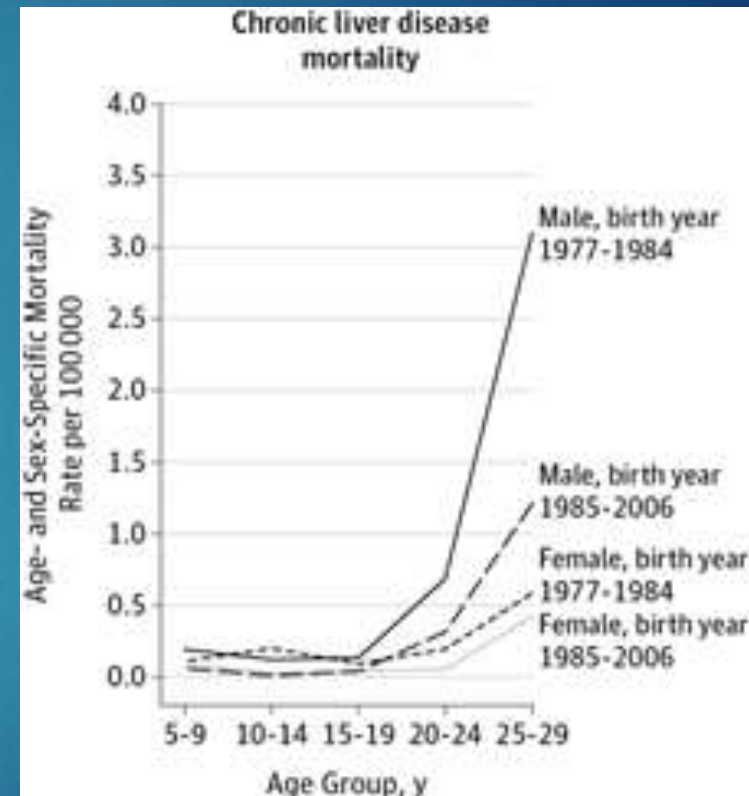
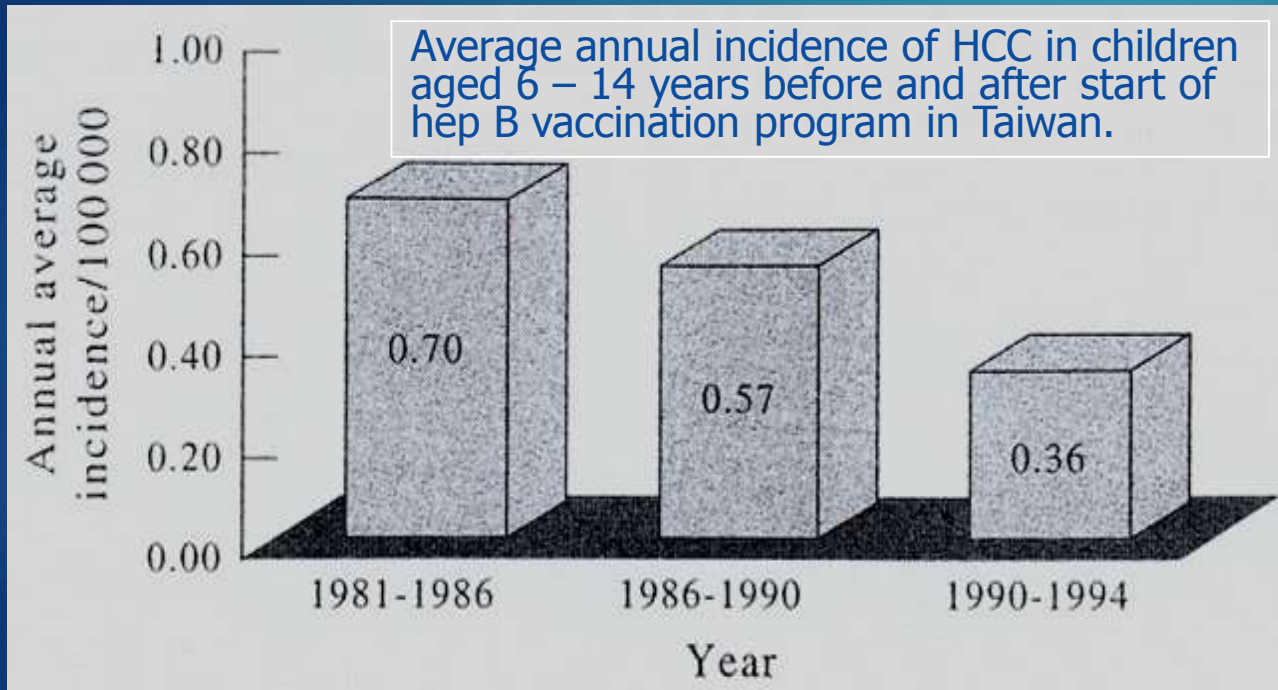
South East Asia	Thailand
	India
	Bangladesh
Western Pacific Region	China
	South Korea
	Malaysia
	Singapore



On a global level, HBsAg prevalence was 3.6%

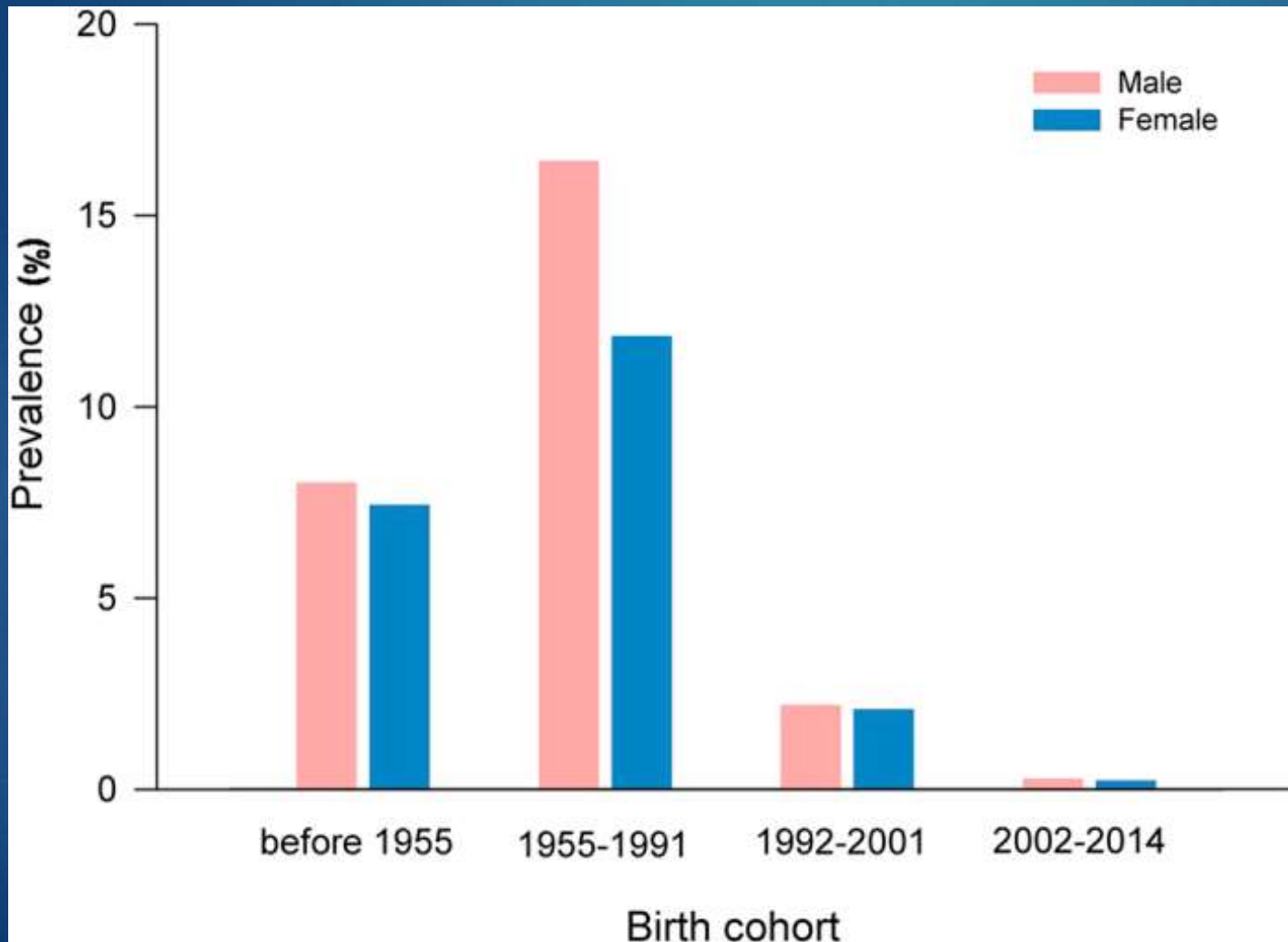
WHO: Asia has the highest HBsAg prevalence (> 8%) in the adult population

# Decreasing HCC incidence and chronic liver disease mortality amongst the young in Taiwan

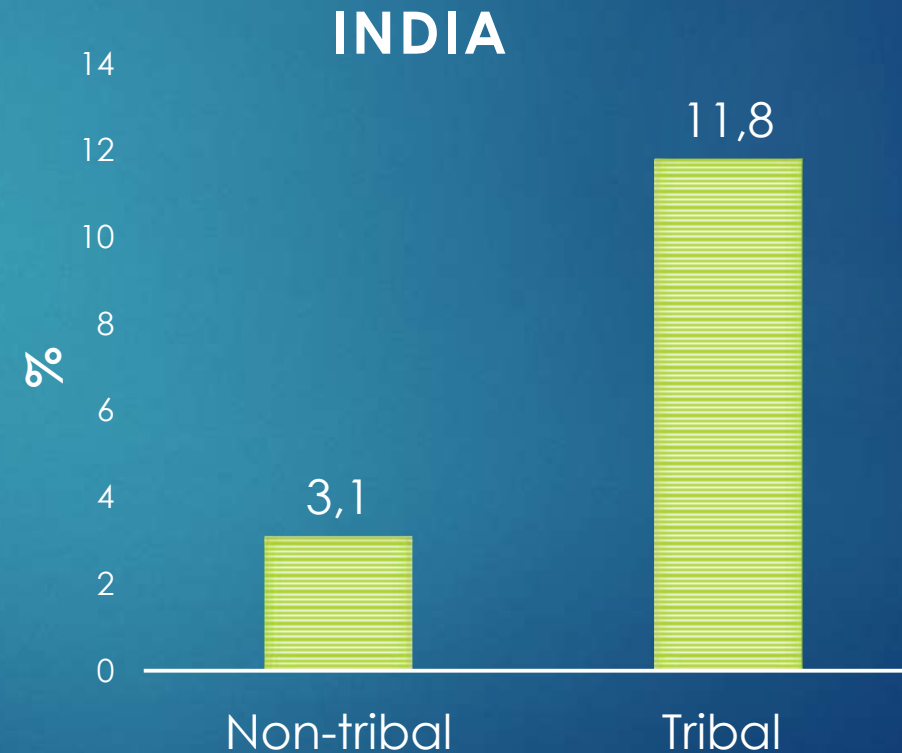
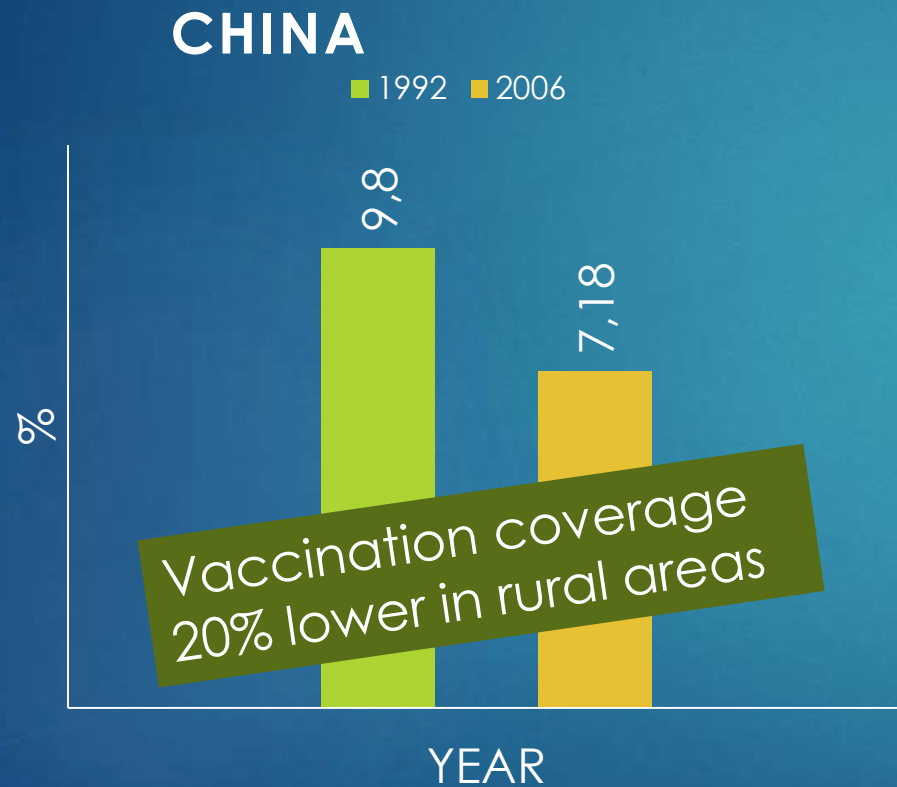


- Strong association of hepatitis B with HCC in children
- Decline in incidence in HCC has correlated well with the decrease in prevalence of HBsAg

# HBsAg prevalence of 0.15 million residents in South China, Guangdong



# Heterogeneity in HBsAg prevalence within a country / region



# HBsAg prevalence, HBV genotype distribution & molecular variants in Asian countries

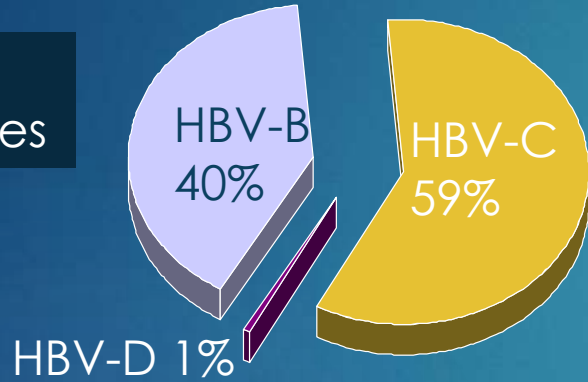
Countries	HBsAg-positive prevalence	HBV genotype distribution
Cambodia	4.6%	A: India
China	7.18%	A1 India
Gaza Strip	3.5%	B: China
India	3.7%	B2 southern China
Iraq	0.6%	C: China
Jordan	1.4%	C1 southern China, India
Kazakhstan	3.8%	C2 northern China
Kuwait	3.5%	D: Arabian countries and India
Saudi Arabia	1.5%-2.6%	D1 Persian Gulf (Iran, Syria, Turkey), India, Pakistan D2, D3, D4, D9 India
Singapore	3.6%	C/D1-CD2 western China
South Korea	4.0%	
United Arab Emirates	2%-7%	
Yemen	5.1%	

4.2% were HBeAg positive; but many have HBeAg-negative viraemia

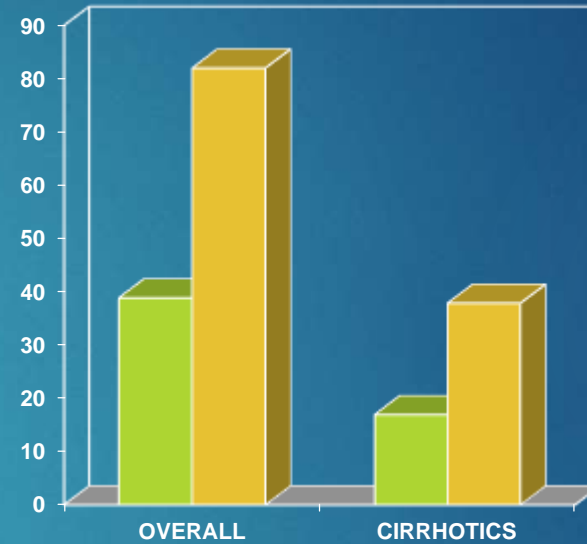
R Zampino et al.  
World J Gastroenterol 2015

# The HBV genotypes of the HBV infected population in Singapore

HBV genotypes



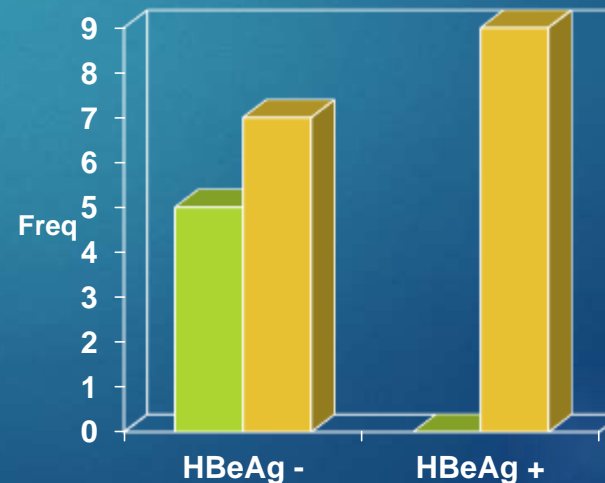
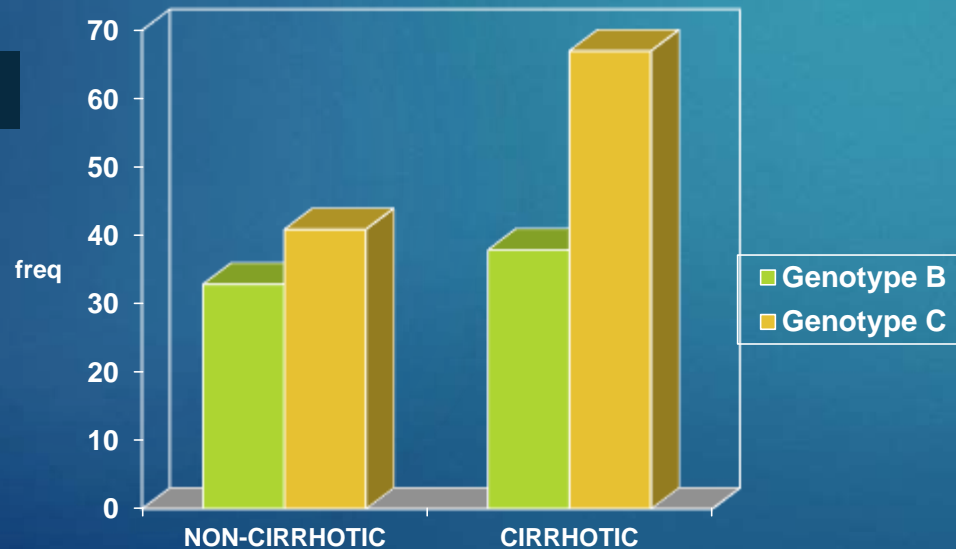
Freq



HBeAg +

Genotype B  
Genotype C

Cirrhosis

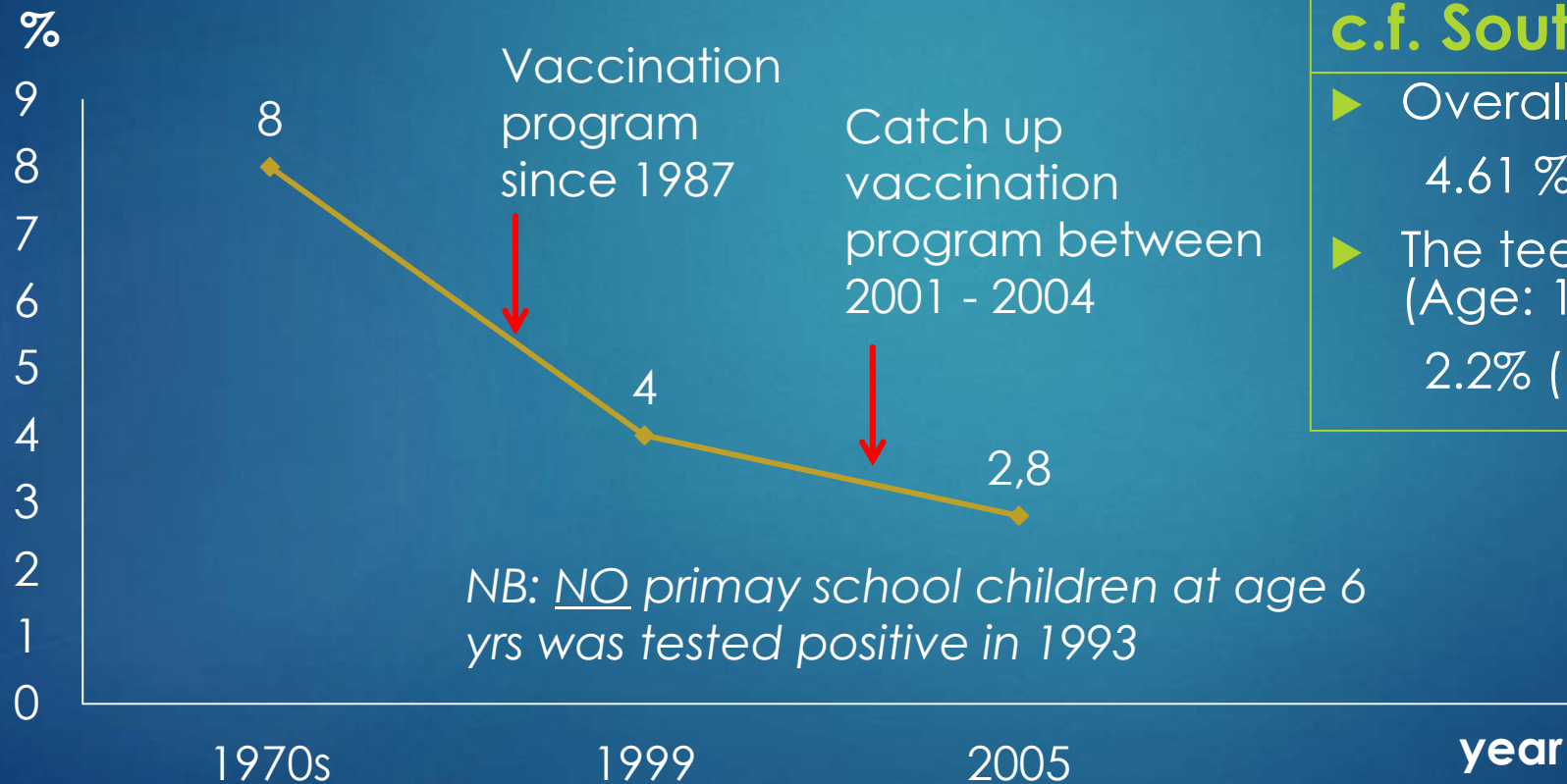


HCC

Genotype B  
Genotype C



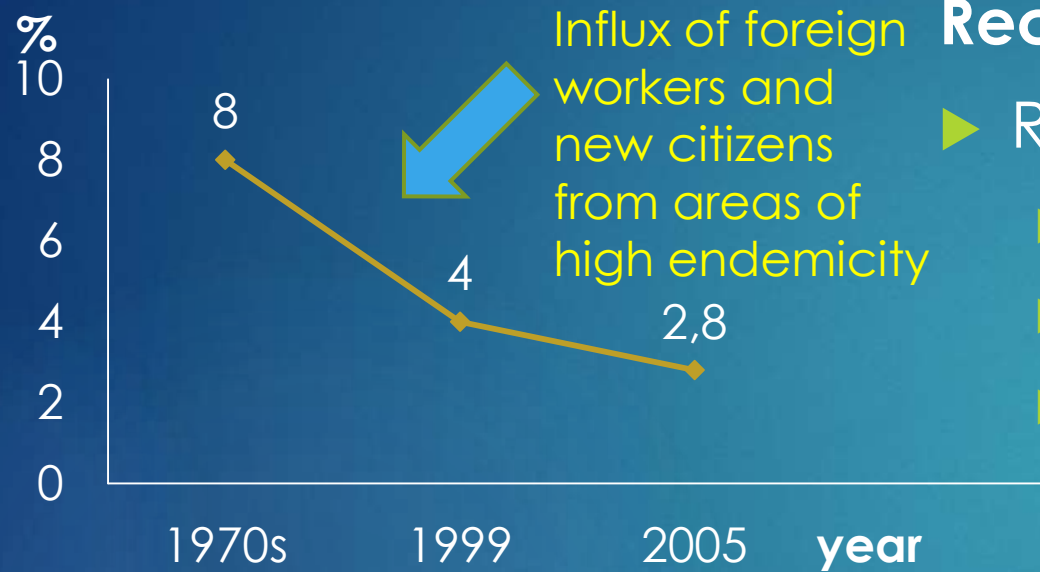
# Age-standardised seroprevalence of hepatitis B (HBsAg) in Singapore



## c.f. South Korea

- ▶ Overall HBsAg prevalence  
4.61 % (1998) to 2.98% (2010)
- ▶ The teenage population (Age: 10-19 years) :  
2.2% (1998) to 0.12% (2010)

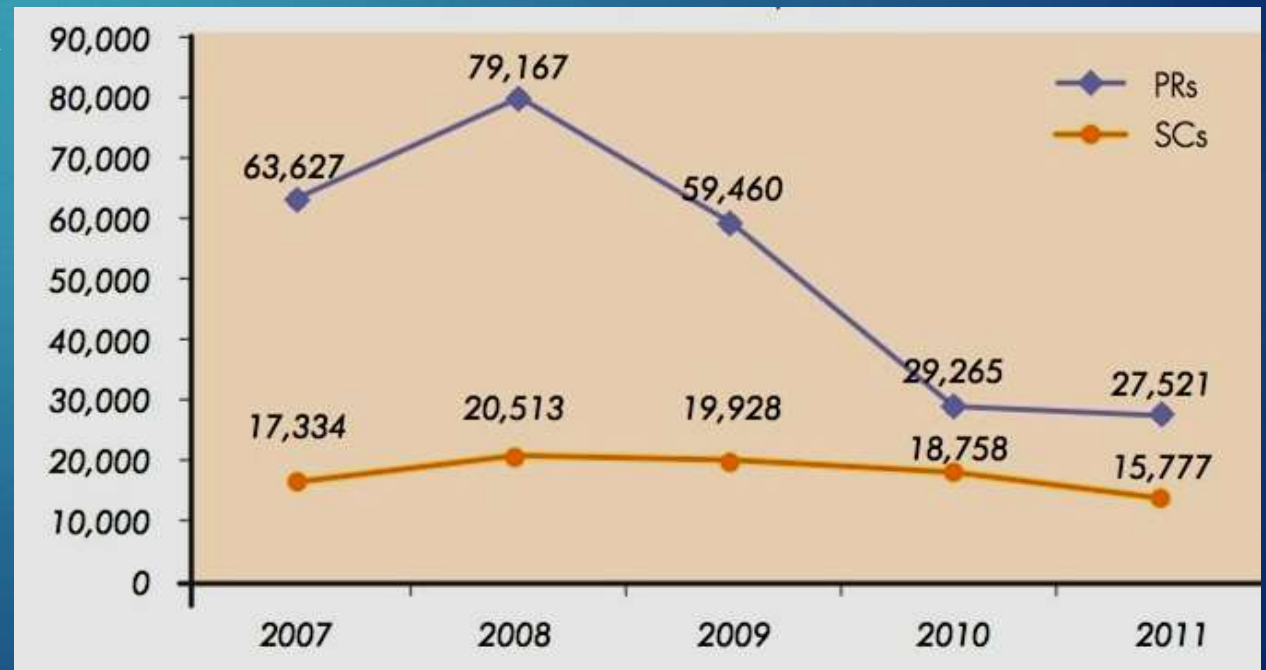
# The HBV infected population in Singapore what are not accounted for in previous studies?



## Recent changes in demographics in Singapore

- ▶ Recent sharp growth of population
  - ▶ 5.26 million in year 2012
  - ▶ 3.27 mil citizen + 0.54 mil PR = 3.81 million
  - ▶ 1.46 mil non-resident population

Numbers given Singapore citizenship and Permanent residency between years 2007 - 2011



**J Hepatol. 1996 Nov;25(5):639-43.**

**Post-transfusion hepatitis type B following multiple transfusions of HBsAg-negative blood.**

Saraswat S et al.

Conclusions There is indirect evidence that incomplete immune control is involved in the **occurrence of OBI in Asian blood donors infected** with genotypes B and C as observed in Europe with genotype A2 but to a lower extent than with genotype D. A post-transcriptional mechanism may play a role in HBsAg expression in some OBIs irrespective of HBV genotype.

**Gut 2012 Dec**

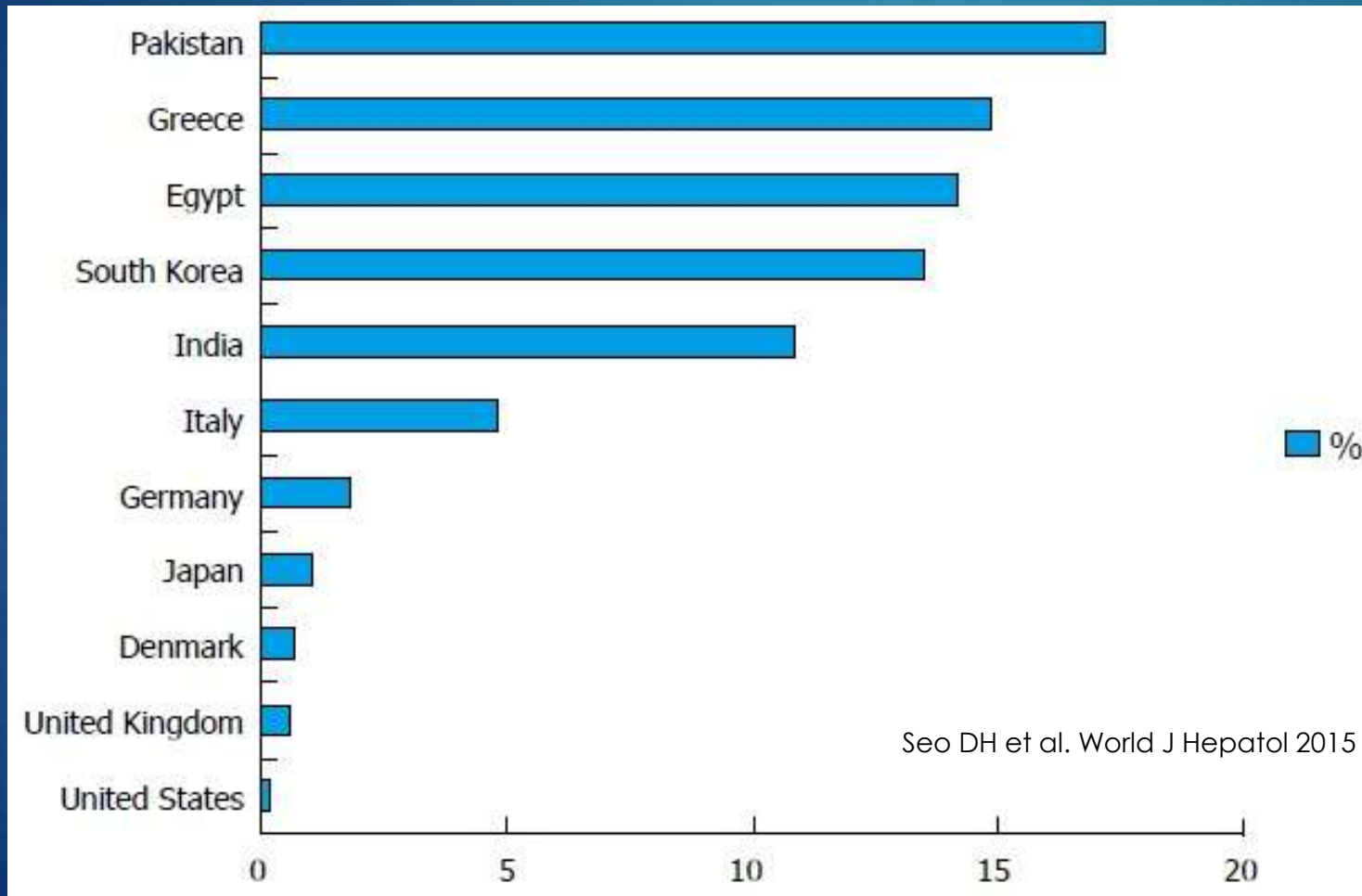
**Occult hepatitis B infection in blood donors from South East Asia: .....**

Daniel Candotti et al.

Results: We found that **six of the 41 patients (14.6%) developed post-transfusion hepatitis**; four of them (66.6%) developed icteric post-transfusion hepatitis B.....These six recipients received a total of 48 units of blood and 30 of these 48 units could be subjected to HBV DNA amplification by polymerase chain reaction. Eleven donor samples were polymerase chain reaction positive and had been transfused to three of the four patients who had developed post-transfusion hepatitis B.

Conclusions: We conclude that post-transfusion hepatitis B continues to be the most common cause of post-transfusion hepatitis in India. **Screening of donor units for HBsAg by ELISA does not exclude all blood units infectious for hepatitis B virus.....**

# Prevalence of anti-HBc antibody in blood donors



In Cambodia:

- ▶ HBsAg prevalence 4.6% in the adult population and 6.3% amongst blood donors
- ▶ C.f. Anti-HBc prevalence were 58.6 – 72.4%

# Summary (I)

- ▶ The prevalence of HBV infection is decreasing in our population
  - ▶ Still seen in the older adult population
  - ▶ Persistence of at-risk population – yet to be covered by vaccination
- ▶ The conventional markers for active HBV infection / replication may be misleading
  - ▶ Precore / core-promoter mutation and HBs mutant (occult infection)
- ▶ Not all HBV are exactly the same
  - ▶ Pathogenicity, natural history and treatment options may differ by genotypes



Management of recipients who  
were exposed to HBV-infected  
blood products

# Recipients exposed to HBV-infected blood products

The clinical outcome will be determined by:

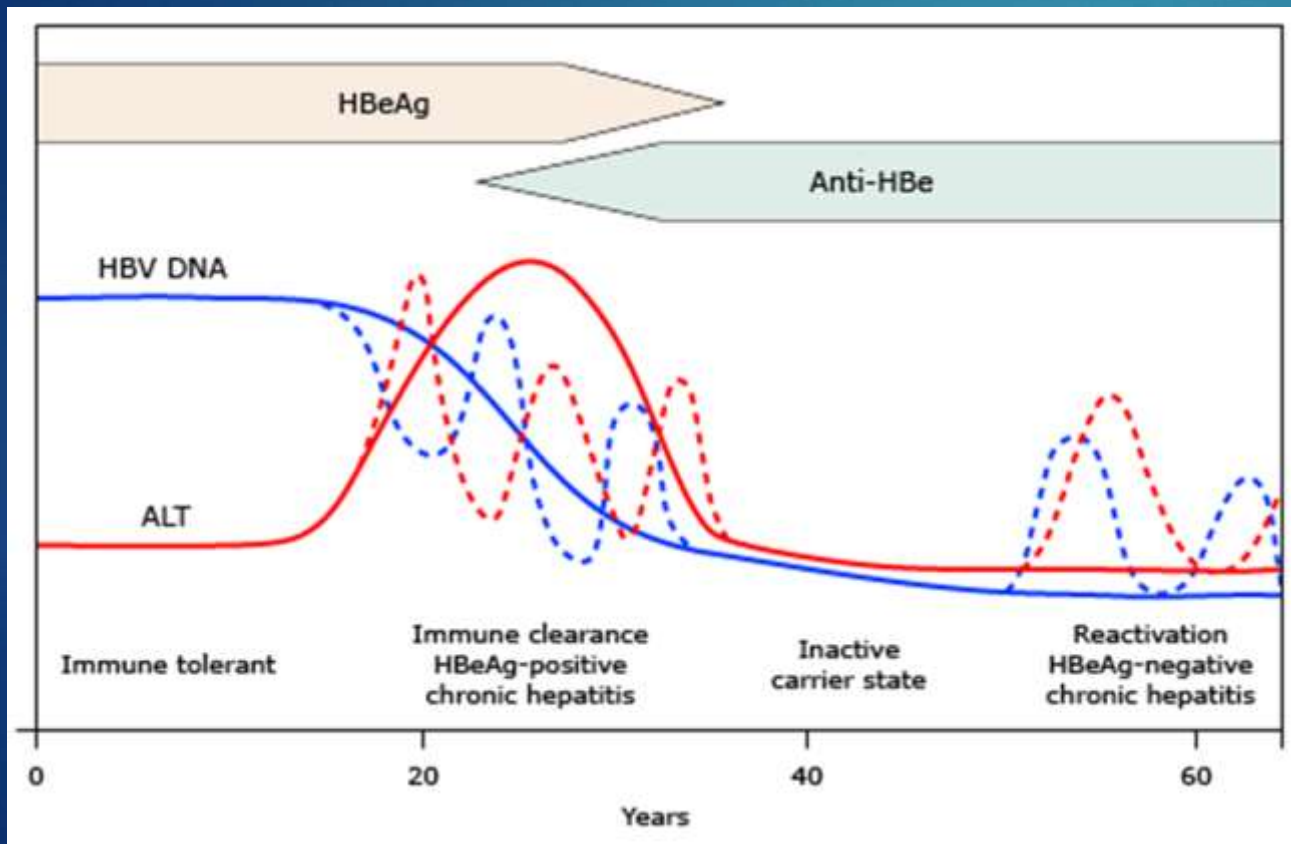
- ▶ Host factors (the recipient)
  - ▶ Previously vaccinated?
  - ▶ Immuno-compromised v.s. otherwise normal patient
- ▶ Viral factors
  - ▶ HBV genotype / variants
  - ▶ Viral load (HBV DNA)

# Likely natural history post-HBV exposure and the appropriate response

Possible clinical outcome	Appropriate response
Subclinical infection (asymptomatic)	Ensure complete resolution of HBV infection
Acute hepatitis B	<ul style="list-style-type: none"><li>- Expectant</li><li>- KIV anti-viral treatment if development of acute severe hepatitis / fulminant hepatic failure</li><li>- KIV liver transplantation</li></ul>
Persistent HBV infection / Chronic hepatitis B	<ul style="list-style-type: none"><li>- Anti-viral (P.O.) versus (s/c) pegylated interferon injection, where appropriate</li><li>- Treatment of complications, and KIV liver transplantation, if indicated.</li></ul>



# Natural history of chronic hepatitis B, at later time of acquisition)



Lok AS et al. Hepatology 2006; 43: S173–S181

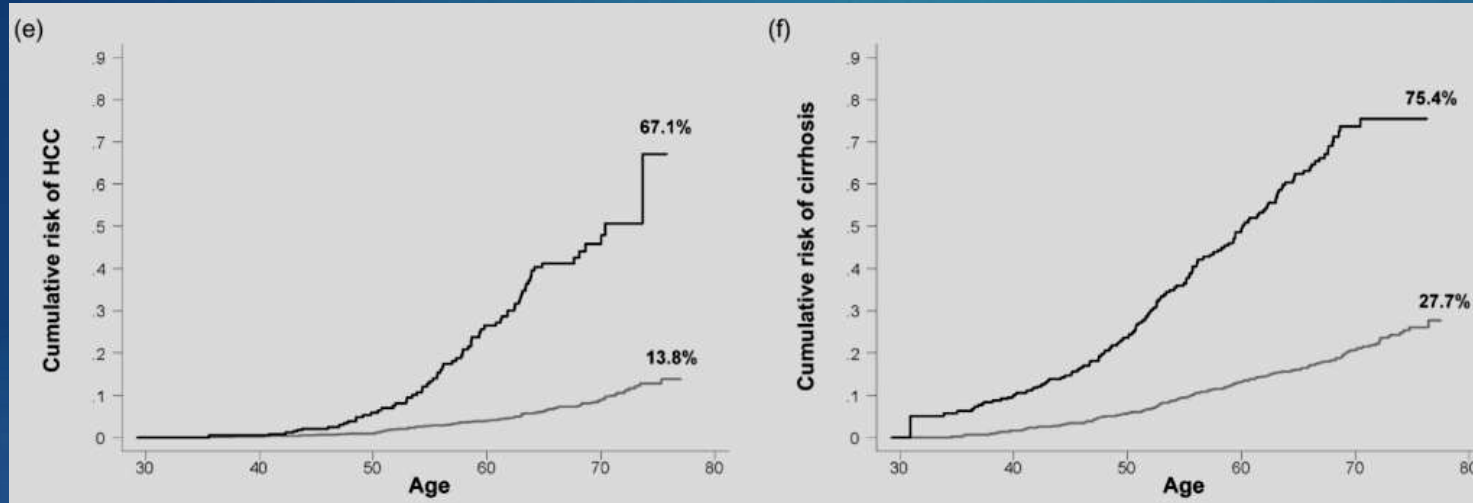
## Effects of NAFLD on treatment of chronic hepatitis B (entecavir)

Variables	With steatosis (n = 65, 30.5%)	Without steatosis (n = 148, 69.5%)	p
<b>24 week</b>			
HBV-DNA clearance (n, %)	31 (47.7%)	87 (58.8%)	0.01
HBeAg seroconversion (n, %)	10 (15.4%)	23 (15.5%)	0.28
ALT normalization (n, %)	26 (40.0%)	65 (43.9%)	0.11
<b>48 week</b>			
HBV-DNA clearance (n, %)	35 (53.8%)	100 (67.6%)	0.04
HBeAg seroconversion (n, %)	12 (18.5%)	33 (22.3%)	0.11
ALT normalization (n, %)	38 (58.5%)	105 (70.9%)	0.04
<b>96 week</b>			
HBV-DNA clearance (n, %)	42 (64.6%)	115 (77.7%)	0.04
HBeAg seroconversion (n, %)	16 (24.6%)	42 (28.4%)	0.13
ALT normalization (n, %)	49 (75.4%)	129 (87.2%)	0.03

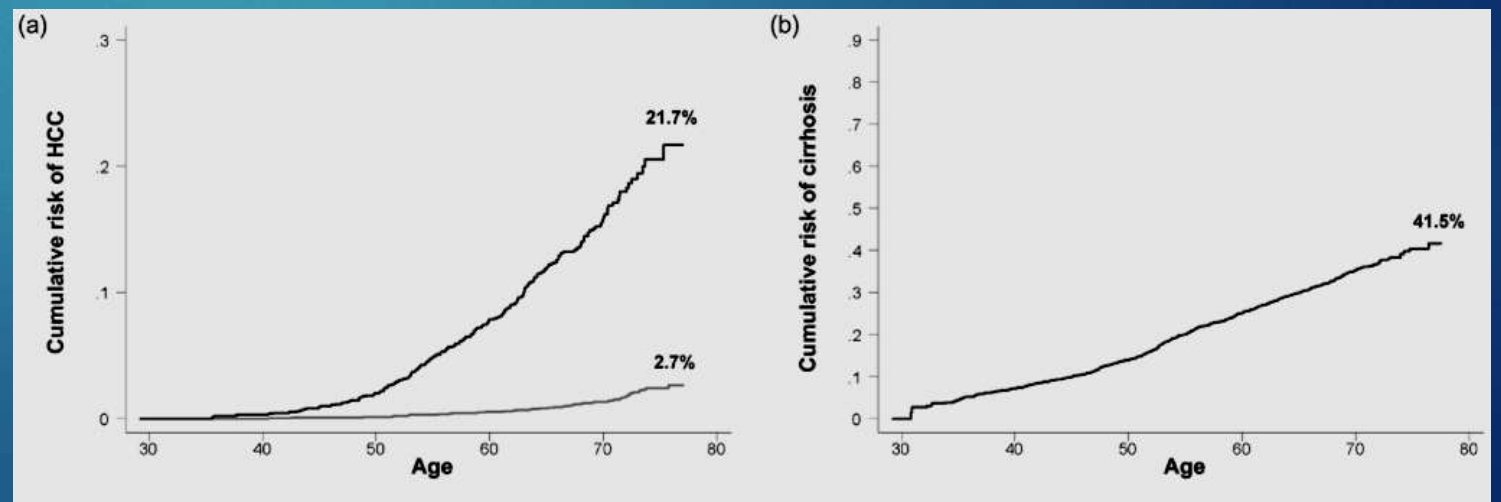
Jin X et al. PLoS One 2012

# Risk of cirrhosis & HCC

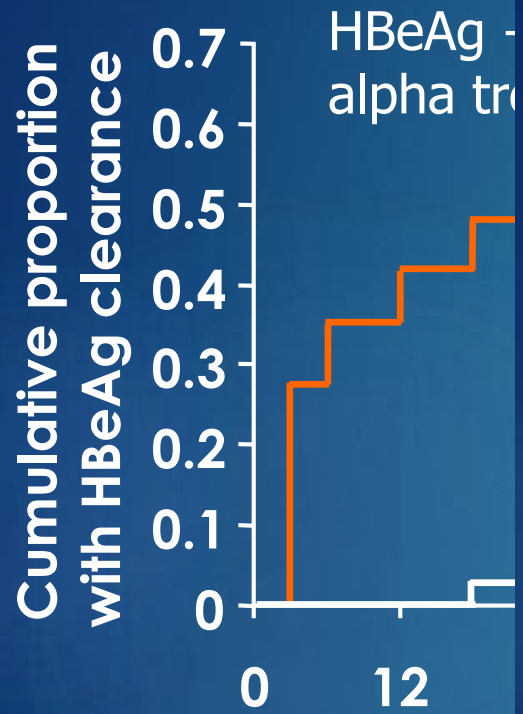
HBeAg positive & negative subjects



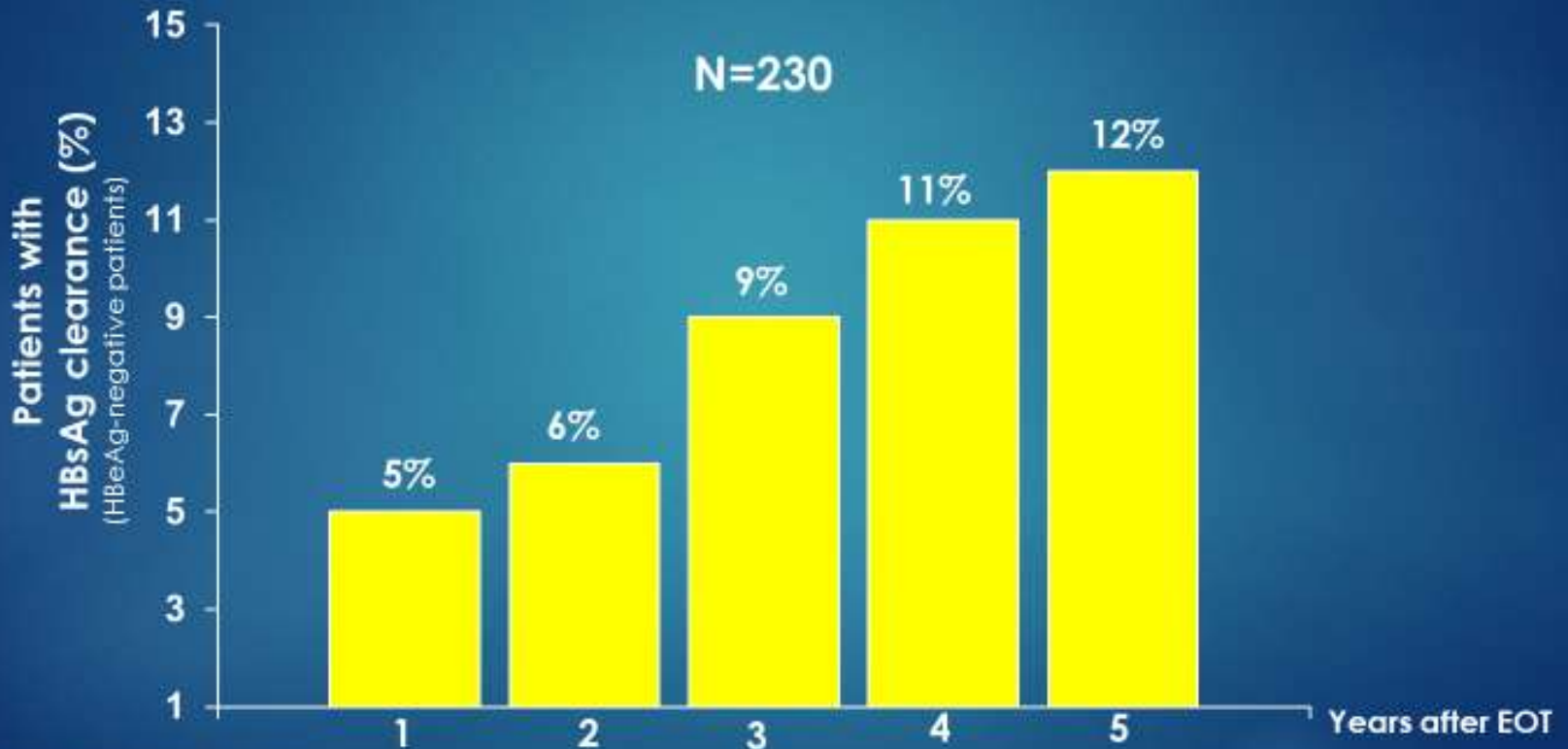
HBsAg positive & negative subjects



# Long – term outcome following (peg-) interferon therapy



HBsAg clearance post-treatment with PEGASYS ± lamivudine



Marcellin et al. APASL 2009

\*Long term response in  
†Treatment duration: 4–

Niederau et al. *N Engl J Med.* 1770.

# Outcome post - interferon alpha therapy for HBeAg + CHB on long-term follow-up\*

- Meta-analysis of 12 studies (n=1975)
- 765 interferon treated / 1210 untreated
- Follow-up range: 2.1–8.9 yrs (mean 6.1)†

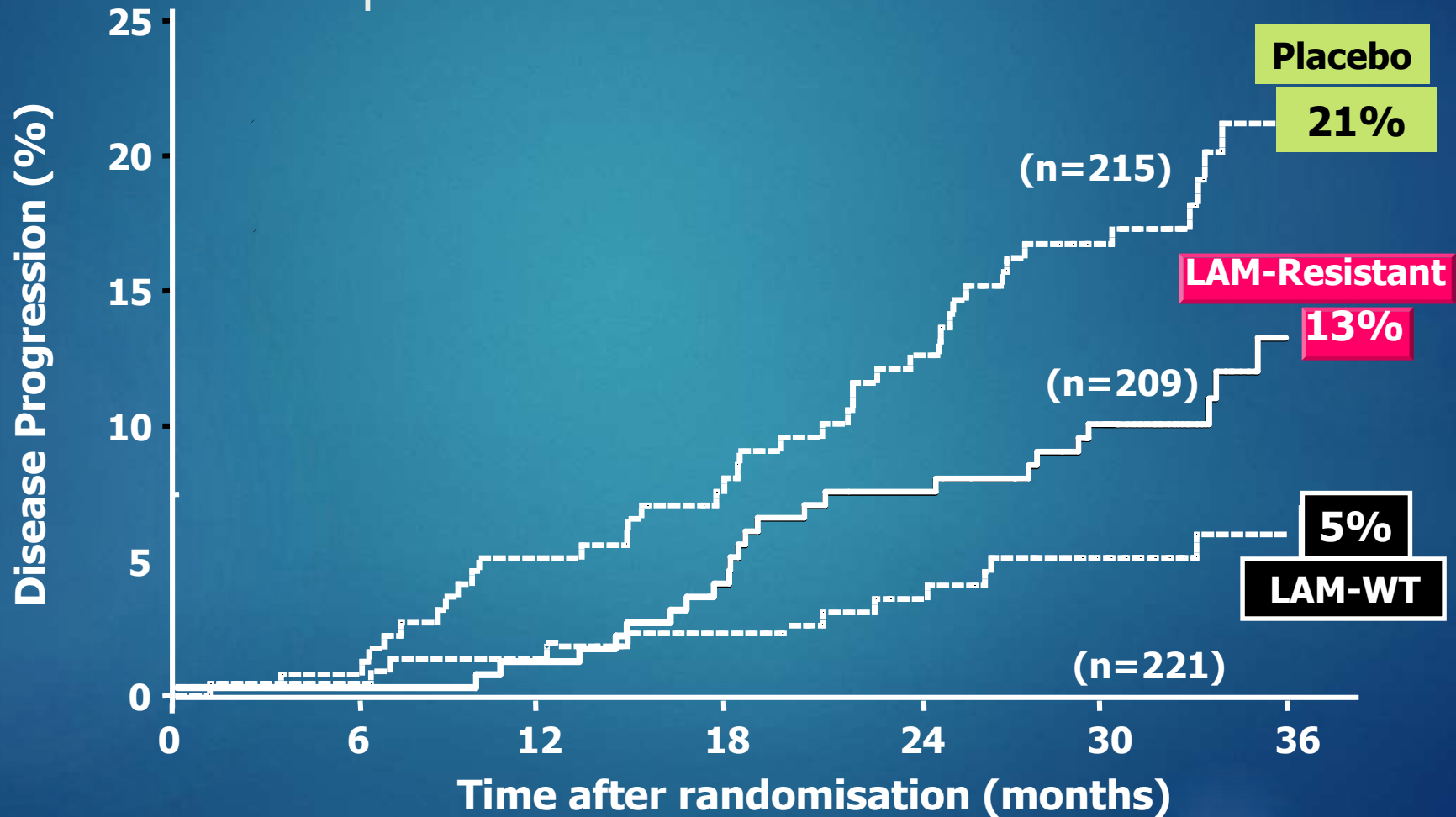
Distribution of probabilities:

	Interferon	Untreated
Loss of HBsAg	11.4%	2.6%
Disease decompensation	9.9%	13.3%
Development of HCC	1.9%	3.2%
Liver-related death	4.9%	8.7%

\*Long-term response in treatment-free follow-up

†Treatment duration: 4–6 months

# Benefits of lamivudine treatment in preventing complications of advanced chronic hepatitis B



# Management of hepatitis B by eliminating HBV infection: preventive measures

- ▶ Universal vaccination
  - ▶ Note: Efficacy drops in the older adults
- ▶ Follow-up on the newly diagnosed HBV infected individuals and manage them accordingly
- ▶ Other modalities of stopping HBV transmission
  - ▶ Tenofovir for HBV – infected pregnant mothers, to prevent vertical transmission

# Summary (II)



- ▶ Prevention is better than cure for the management of HBV infection.
- ▶ If a blood-product recipient was exposed to HBV, the urgency and the extent of management required is dependent on the recipient's response to the infection and his / her background / baseline conditions. Follow-up of outcome of infection is important.
- ▶ If urgent treatment is required, oral anti-viral should be the drug of choice, with view of liver transplantation, if indicated.
- ▶ For those who develop chronic hepatitis B, pegylated interferon infection or oral anti-viral may be considered, based on individual patient's condition, with the aim of disease control, prevention of long term complications and, in small proportion of cases, treatment-free sustained viral response.